pounds. Amidobenzene and nitrobenzene are less active in producing rigor.

The respiration is considerably and early affected in warm-blooded animals (cats) by benzene and its compounds. There is usually a primary acceleration, followed by slowing. The heart appeared to stop before the respiration in poisoning by benzene and its haloid compounds, by ethylbenzene, amidobenzene, and nitrobenzene, whilst respiration usually failed before the heart, or nearly at the same time, in poisoning by the methylbenzenes and oxybenzenes.

The first effect of the benzene compounds on the pulse or on blood pressure is usually a quickening of the pulse and a rise in the pressure. This is followed by slowing of the pulse and fall of the pressure.

In their preliminary communication in 1887, the authors directed attention to the curious resemblance between the tremor caused by benzene and some other aromatic substances in frogs and the symptoms of disseminated sclerosis in man. In the present paper, they point out also the likeness between the violent slapping movements caused in the frog by some of the haloid compounds of benzene, as well as by amidobenzene, and the symptoms of locomotor ataxy in man.

IV. "The Physiological Action of the Paraffinic Nitrites considered in connexion with their Chemical Constitution. Part I. The Action of the Paraffinic Nitrites on Blood Pressure." By J. Theodore Cash, M.D., F.R.S., Professor of Materia Medica in the University of Aberdeen, and Wyndham R. Dunstan, M.A., Professor of Chemistry to the Pharmaceutical Society of Great Britain. Received March 4, 1891.

(Abstract.)

CONTENTS.

The present investigation was commenced three years ago, in order to throw further light on the mode of action of the paraffinic nitrites when introduced into the animal organism, and particularly to deter-

mine in what manner this action is conditioned by the different chemical constitution of the various nitrites employed. Since the chemical constitution of these compounds is well established, and their molecules are comparatively simple in structure, and, moreover, as their principal physiological effects are capable of accurate quantitative study, it seemed likely that the inquiry would furnish valuable pharmacological results.

Our knowledge of the physiological behaviour of the organic nitrites has been almost wholly derived from the study of amyl nitrite, which has been observed to produce a similar but far greater effect than its lower homologue ethyl nitrite, whose action, however, has not hitherto been so closely examined as that of the amyl compound. Unfortunately it seems certain that the results which have been obtained with amyl nitrite are to a large extent vitiated by the circumstance that, as a rule, insufficient pains have been taken to procure the nitrite in a chemically pure state, whilst, in addition, the usual mode of administration has been such that it is impossible to determine exactly how much of the compound has actually been inhaled.

It is believed that both these sources of error have been obviated in the present research. The exact composition of each substance was known, and a special apparatus was devised for ensuring the inhalation without loss of a definite amount of nitrite, through the trachea in animals, and through the nostrils in the human subject.

In this, the first part of the communication, an account is given of the principal work which has already been done on this subject, and this is followed by a brief description of the method by which the nitrites have been prepared and their purity ascertained. The physiological actions which have been made the subject of special study are those on blood pressure, pulse, and respiration, whilst the action on striated muscular fibre has also been fully examined. The present paper deals almost entirely with the action of various nitrites on blood pressure, and with the special apparatus used in studying it. A subsequent paper will have reference to the action of these same nitrites in producing contraction of striated muscle, and will conclude with a discussion of the whole of our results, both in their chemical and physiological aspects.

The nitrites have been prepared by the reaction of the corresponding alcohol, previously purified, with sodium nitrite in the presence of dilute acid. This has proved to constitute a satisfactory plan of preparing the entire series of nitrites with which we have worked. The liquid nitrites, after having been thoroughly washed and dried, were repeatedly distilled, in some cases under reduced pressure, until a liquid boiling at a constant temperature was obtained. Proof that the liquids thus obtained had the composition of the required nitrites

was furnished by analysis. The nitrites which we have prepared are those of methyl, ethyl, primary propyl, secondary propyl, primary butyl, secondary butyl, tertiary butyl, isobutyl, α-amyl, β-amyl, and tertiary amyl. Certain of these nitrites were prepared by us for the first time, while of those which had already been described some have been found to possess different physical properties to those usually ascribed to them. For the purposes of administration, a known volume of each nitrite was taken. The relative density of each substance having been previously determined, the weight corresponding to the volume taken was readily calculated, and from this was ascertained the amount of the active nitrite group (NO_2) present.

The apparatus for recording alterations in blood pressure consisted of a mercurial manometer writing upon a slowly rotating drum, and a Fick's kymograph writing upon a more rapidly revolving Balzac's cylinder. These manometers could be employed together or separately, but, as a rule, when pressure and number of pulsations only were being observed, both were kept open. The advantage of the arrangement is that a considerable period of time is represented by a short lineal movement on a small drum, whilst on the quick one the pulse can be reckoned and the course of the rapidly occurring variations of pressure studied. Respiration was recorded on a registering Marey's tambour attached to a double tambour placed on the thorax of the animal. An electrical signal, in connexion with a key and Daniell's cell, was placed beneath the point recording the blood pressure in order to mark the time of administration of nitrite. In cases where vagus, splanchnic, or sciatic stimulation was employed, a double key admitted the faradic current from the secondary coil of a du Bois-Reymond's inductorium to the electrodes on which the nerve rested, while at the same time it closed the signal circuit indicating the length of stimulation.

The following represents the course of the nitrite administration. The blood pressure being steady, the clockwork of the quick drum was started so as to bring it up to full speed before the cylinder was made to rotate by screwing up the friction wheel. The nitrite was then introduced into the side tube of the inhaler; an arrangement of valves permitted inspiration only to take place through this tube. The cylinder was started, and after a sufficient record of the pulse and respiration for the time being had been recorded, the nitrite was administered, the time of administration being recorded. A sufficient time having elapsed for inhalation, the air-tube of the inhaler was opened, the quick drum being permitted to run as long as was necessary for the purpose of recording the changes in pulse and pressure. During the recovery of pressure an occasional record of pulse and respiration was taken on the quick drum, corresponding marks being made on the slowly revolving cylinder.

It is well established that small doses of amyl nitrite cause a fall of blood pressure, resulting chiefly, if not entirely, from a powerful dilatation of the arterioles, reducing peripheral resistance to a great extent. Two distinct views have been advanced as to the cause of the dilatation. Filehne maintains that his experimental results demonstrate the dilatation to be due, not to a local action on the walls of the vessels, but to the direct action of the nitrite on the vaso-motor centres. On the other hand, Brunton, and also Mayer and Friedrich, believe they have shown that the dilatation is the result of a direct action on the walls of the vessel, and is independent of any effect on the central nervous system.

After discussing the experiments of Filehne, Brunton, and Mayer, an account is given of the experiments made by the authors to elucidate this question. These were made with cats, but control experiments with rabbits afforded the same results. In the first series the head of the animal was entirely cut off from the circulation, yet inhalation of pure amyl nitrite ($\frac{1}{38}$th c.c.) caused a rapid fall of pressure, the lowest point reached exactly corresponding with that noticed in an immediately preceding experiment, in which the head was included in the circulation. In the second series all the arteries passing to the head were temporarily ligatured, and salt solution containing dissolved amyl nitrite ($\frac{1}{38}$th c.c.) injected through the distal end of the carotid artery, one of the jugular veins being opened so as to admit of an escape of blood and hinder the production of a possibly abnormal intravascular tension in the brain. The same effect was constantly observed; the blood pressure rose, and not until the clamps were removed did the fall of pressure of the usual character occur. There is thus no indication of the characteristic nitrite effect, so long as the vessels are ligatured, although the nitrite must have passed to the medulla oblongata by vascular anastomosis, and therefore to the chief vaso-motor centre. By the injection of Berlin blue, it was demonstrated that access could be gained to the medulla through this channel. The conclusion that the nitrite effect is the result of an action on the vessels, and not on the central nervous system, was confirmed by observations on the effect produced by nitrites after splanchnic stimulation and section. Splanchnotomy is attended with a considerable reduction of pressure, and if nitrite be administered when this is at its minimum, a further reduction occurs, which, however, is not so great as that observed before section. But if administration of nitrite be delayed until the occurrence of one of the temporary elevations of pressure which are observed from time to time, the fall of pressure closely approximates to that produced before splanchnotomy. Simultaneous splanchnic stimulation and nitrite inhalation also cause a normal fall in pressure.

In experiments with the human subject, an accurate record was

taken of the pulse-rate, after inhalation of a known quantity of nitrite. A mask inhaler was specially devised, so as to avoid loss of substance during inhalation. It consisted of a conical metal box covering the mouth, and fitting accurately on the bridge of the nose by the aid of a hollow rubber border, which could be distended by injection of air. It is provided with three tubes opening out of a common trunk in the front of the mask; one of these was not furnished with any valve, but the two lateral tubes had each one valve, opening inwards and outwards respectively. The tube intended for the inspiration of nitrite had a continuation of india-rubber, in the middle of which a glass bulb was inserted for the reception of the nitrite. Spring clamps were placed on either side of the bulb. The mask having been adjusted to the face, and respiration being regular through the valvular tube, the drum was started at full speed so as to record the normal pulse rate, and the inhalation tube was opened by removing the clamps on either side of the bulb at the same time as the interior tube was closed. The time of inhalation was recorded by a signal marker.

There is a considerable variation on the part of individuals to nitrite effect, the acceleration of the pulse in the case of those of neurotic tendency being much greater, and the time of its continuance much less than in that of a lymphatic subject. The order of activity (extent of acceleration) for various nitrites deduced from a large number of experiments is (1) α-amyl; (2) β-amyl; (3) isobutyl; (4) secondary butyl; (5) primary butyl; (6) secondary propyl; (7) primary propyl; (8) ethyl; (9) methyl.

The action of each paraffinic nitrite has been closely contrasted with that of amyl nitrite. The results may be broadly summarised as follows:—

All the nitrites examined produce, in whatever way administered, a reduction of blood pressure, variable, however, according to the compound employed in its extent and in its progress, as well as in the ensuing recovery.

A pulse acceleration usually accompanies and succeeds the fall upon inhalation, the extent of inhalation varying in the case of individual nitrites. The acceleration is less upon intra-vascular injection, especially intra-arterial injection, than when administration is by inhalation; a distinct retardation of pulse is frequently produced by the former method, especially by carotid injection.

The extent of acceleration appears to be less in the case of cats than in the human subject.

The respiration is affected (1) temporarily during and immediately subsequent to inhalation, in various degrees by the different nitrites, and (2) permanently by the repeated administrations of the same or different nitrites.

As regards the principal effect, reduction of blood pressure, the activity (extent of reduction) of the various nitrites takes the following order when equal volumes are administered to animals by inhalation:—(1) secondary propyl; (2) tertiary butyl; (3) secondary butyl, (4) isobutyl, nearly equal; (5) tertiary amyl; (6) α-amyl, (7) β-amyl, nearly equal; (8) methyl; (9) butyl; (10) ethyl; (11) propyl.

The order is somewhat modified when the nitrites are given by intra-vascular injection. When the duration of the sub-normal pressure is considered, the order is nearly the reverse of that given above, the effect of methyl nitrite being the last, and that of secondary propyl nitrite one of the first, to disappear. In contrasting the results of the measurement of pulse acceleration produced by these nitrites, it is noticed that their activity in this respect does not follow the same order as that in reducing blood pressure, the amyl nitrites in particular occupying a higher position in the table. The causes of these differences will be considered in the second part of this paper, in conjunction with a discussion of the relation of the chemical constitution of the nitrites to the physiological effects now described, and also to those produced in striated muscle, a description of which will form part of the subsequent communication.

In order that the physiological data might be placed on an absolutely satisfactory basis for chemical discussion, we determined at the commencement of last year to repeat all the more important physiological experiments. This necessitated the labour of preparing fresh specimens of the nitrites. The results of these confirmatory experiments have been in every respect satisfactory, since they differed in no important respect from those previously obtained.

The chemical part of this enquiry has been conducted in the Research Laboratory of the Pharmaceutical Society, in London, whilst the physiological experiments have been made in the Pharmacological Laboratory of the University of Aberdeen.

V. "Some Points in the Structure and Development of Dentine." By J. Howard Mummery. Communicated by C. S. Tomes, F.R.S. Received February 7, 1891.

(Abstract.)

The purpose of the present paper is to show that there are appearances in dentine which suggest that it is formed by a connective tissue calcification, and that the process is more closely analogous to the formation of bone than has usually been supposed.

The varied theories held as to the structure and development of